(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
3 January 2003 (03.01.2003)

PCT

(10) International Publication Number
WO 03/000308 A1

(51) International Patent Classification[7]: A61L 31/16, A61F 2/06

(21) International Application Number: PCT/US02/19889

(22) International Filing Date: 21 June 2002 (21.06.2002)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
09/887,464 22 June 2001 (22.06.2001) US

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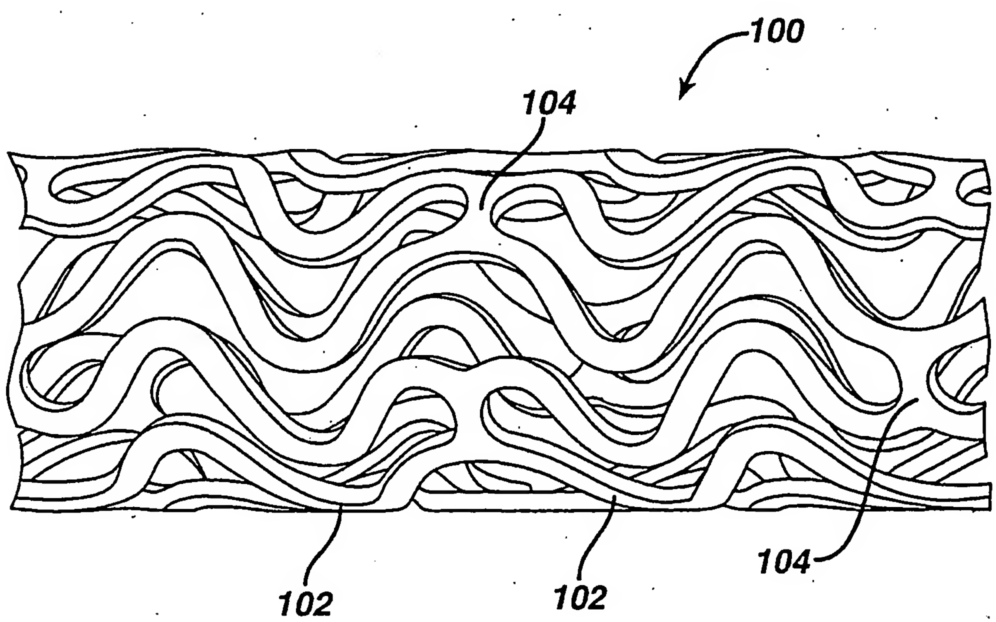
(81) Designated States (*national*): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZM, ZW.

(84) Designated States (*regional*): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*
— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: DRUG DELIVERY DEVICES



(57) Abstract: Local drug delivery medical devices are utilized to deliver therapeutic dosages of drugs, agents or compounds directly to the site where needed. The local drug delivery medical devices utilize various materials and coating methodologies to maintain the drugs, agents or compounds on the medical device until delivered and positioned.

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procedure is attributable to its relatively high success rate and its minimal invasiveness compared with coronary bypass surgery. A limitation associated with percutaneous transluminal coronary angioplasty is the abrupt closure of the vessel which may occur immediately after the procedure and restenosis which occurs gradually following the procedure. Additionally, restenosis is a chronic problem in patients who have undergone saphenous vein bypass grafting. The mechanism of acute occlusion appears to involve several factors and may result from vascular recoil with resultant closure of the artery and/or deposition of blood platelets and fibrin along the damaged length of the newly opened blood vessel.

Restenosis after percutaneous transluminal coronary angioplasty is a more gradual process initiated by vascular injury. Multiple processes, including thrombosis, inflammation, growth factor and cytokine release, cell proliferation, cell migration and extracellular matrix synthesis each contribute to the restenotic process.

While the exact mechanism of restenosis is not completely understood, the general aspects of the restenosis process have been identified. In the normal arterial wall, smooth muscle cells proliferate at a low rate, approximately less than 0.1 percent per day. Smooth muscle cells in the vessel walls exist in a contractile phenotype characterized by eighty to ninety percent of the cell cytoplasmic volume occupied with the contractile apparatus. Endoplasmic reticulum, Golgi, and free ribosomes are few and are located in the perinuclear region. Extracellular matrix surrounds the smooth muscle cells and is rich in heparin-like glycosylaminoglycans which are believed to be responsible for maintaining smooth muscle cells in the contractile phenotypic state (Campbell and Campbell, 1985).

Upon pressure expansion of an intracoronary balloon catheter during angioplasty, smooth muscle cells within the vessel wall become injured, initiating a thrombotic and inflammatory response. Cell derived growth factors such as platelet derived growth factor, basic fibroblast growth factor, epidermal

Lab. Invest. 52: 611-616, 1985; Clowes, A.W. and Clowes, M.M., Circ. Res. 58: 839-845, 1986; Majesky et al., Circ. Res. 61: 296-300, 1987; Snow et al., Am. J. Pathol. 137: 313-330, 1990; Okada, T. et al., Neurosurgery 25: 92-98, 1989), colchicine (Currier, J.W. et al., Circ. 80: 11-66, 1989), taxol (Sollot, S.J. et al., J. Clin. Invest. 95: 1869-1876, 1995), angiotensin converting enzyme (ACE) inhibitors (Powell, J.S. et al., Science, 245: 186-188, 1989), angiopeptin (Lundergan, C.F. et al. Am. J. Cardiol. 17(Suppl. B):132B-136B, 1991), cyclosporin A (Jonasson, L. et al., Proc. Natl., Acad. Sci., 85: 2303, 1988), goat-anti-rabbit PDGF antibody (Ferns, G.A.A., et al., Science 253: 1129-1132, 1991), terbinafine (Nemecek, G.M. et al., J. Pharmacol. Exp. Thera. 248: 1167-1174, 1989), trapidil (Liu, M.W. et al., Circ. 81: 1089-1093, 1990), tranilast (Fukuyama, J. et al., Eur. J. Pharmacol. 318: 327-332, 1996), interferon-gamma (Hansson, G.K. and Holm, J., Circ. 84: 1266-1272, 1991), rapamycin (Marx, S.O. et al., Circ. Res. 76: 412-417, 1995), steroids (Colburn, M.D. et al., J. Vasc. Surg. 15: 510-518, 1992), see also Berk, B.C. et al., J. Am. Coll. Cardiol. 17: 111B-117B, 1991), ionizing radiation (Weinberger, J. et al., Int. J. Rad. Onc. Biol. Phys. 36: 767-775, 1996), fusion toxins (Farb, A. et al., Circ. Res. 80: 542-550, 1997) antisense oligonucleotides (Simons, M. et al., Nature 359: 67-70, 1992) and gene vectors (Chang, M.W. et al., J. Clin. Invest. 96: 2260-2268, 1995). Anti-proliferative action on smooth muscle cells *in vitro* has been demonstrated for many of these agents, including heparin and heparin conjugates, taxol, tranilast, colchicine, ACE inhibitors, fusion toxins, antisense oligonucleotides, rapamycin and ionizing radiation. Thus, agents with diverse mechanisms of smooth muscle cell inhibition may have therapeutic utility in reducing intimal hyperplasia.

However, in contrast to animal models, attempts in human angioplasty patients to prevent restenosis by systemic pharmacologic means have thus far been unsuccessful. Neither aspirin-dipyridamole, ticlopidine, anti-coagulant therapy (acute heparin, chronic warfarin, hirudin or hirulog), thromboxane receptor antagonism nor steroids have been effective in preventing restenosis, although platelet inhibitors have been effective in preventing acute reocclusion after angioplasty (Mak and Topol, 1997; Lang et al., 1991; Popma et al., 1991).

expanded within the lumen of an angioplastied coronary artery, provide structural support through rigid scaffolding to the arterial wall. This support is helpful in maintaining vessel lumen patency. In two randomized clinical trials, stents increased angiographic success after percutaneous transluminal coronary angioplasty, by increasing minimal lumen diameter and reducing, but not eliminating, the incidence of restenosis at six months (Serruys et al., 1994; Fischman et al., 1994).

Additionally, the heparin coating of stents appears to have the added benefit of producing a reduction in sub-acute thrombosis after stent implantation (Serruys et al., 1996). Thus, sustained mechanical expansion of a stenosed coronary artery with a stent has been shown to provide some measure of restenosis prevention, and the coating of stents with heparin has demonstrated both the feasibility and the clinical usefulness of delivering drugs locally, at the site of injured tissue.

As stated above, the use of heparin coated stents demonstrates the feasibility and clinical usefulness of local drug delivery; however, the manner in which the particular drug or drug combination is affixed to the local delivery device will play a role in the efficacy of this type of treatment. For example, the processes and materials utilized to affix the drug/drug combinations to the local delivery device should not interfere with the operations of the drug/drug combinations. In addition, the processes and materials utilized should be biocompatible and maintain the drug/drug combinations on the local device through delivery and over a given period of time. For example, removal of the drug/drug combination during delivery of the local delivery device may potentially cause failure of the device.

Accordingly, there exists a need for drug/drug combinations and associated local delivery devices for the prevention and treatment of vascular injury causing intimal thickening which is either biologically induced, for example atherosclerosis, or mechanically induced, for example, through percutaneous transluminal coronary angioplasty. In addition, there exists a

material being affixed to at least one of the medical device or a delivery system for the medical device.

In accordance with another aspect, the present invention is directed to a local drug delivery apparatus. The local drug delivery apparatus comprises a medical device for implantation into a treatment site of a living organism and at least one agent in therapeutic dosages releasably affixed to the medical device for the treatment of reactions by the living organism caused by the medical device or the implantation thereof, the at least one agent being incorporated into a polymeric matrix. The local drug delivery apparatus also comprises a material for preventing the polymeric matrix from adhering to itself when parts of the medical device make contact with one another.

In accordance with another aspect, the present invention is directed to a drug delivery device. The drug delivery device comprises a medical device for implantation into a treatment site of a living organism, and therapeutic dosages of one or more anti-proliferatives, one or more anti-inflammatories, one or more anti-coagulants, and one or more immunosuppressants releasably affixed to the medical device for the treatment of reactions by the living organism caused by the medical device or the implantation of the medical device at the treatment site.

In accordance with another aspect, the present invention is directed to a method for maintaining agents on a medical device during implantation into a treatment site of a living organism. The method comprises releasably affixing one or more agents in therapeutic dosages to the medical device, treating one of the medical device or the delivery device with a material for preventing the one or more agents from separating from the medical device during delivery and implantation of the medical device at the treatment site, and loading the medical device into a delivery device.

In accordance with another aspect, the present invention is directed to a method for maintaining agents on a medical device during implantation into a

In order to be effective, the drugs, agents or compounds should preferably remain on the medical devices during delivery and implantation. Accordingly, various coating techniques for creating strong bonds between the drugs, agents or compounds may be utilized. In addition, various materials may be utilized as surface modifications to prevent the drugs, agents or compounds from coming off prematurely.

BRIEF DESCRIPTION OF THE DRAWINGS

The foregoing and other features and advantages of the invention will be apparent from the following, more particular description of preferred embodiments of the invention, as illustrated in the accompanying drawings.

Figure 1 is a view along the length of a stent (ends not shown) prior to expansion showing the exterior surface of the stent and the characteristic banding pattern.

Figure 2 is a perspective view of the stent of Figure 1 having reservoirs in accordance with the present invention.

Figure 3 is a cross-sectional view of a band of the stent of Figure 1 having drug coatings thereon in accordance with a first exemplary embodiment of the invention.

Figure 4 is a cross-sectional view of a band of the stent of Figure 1 having drug coatings thereon in accordance with a second exemplary embodiment of the invention.

Figure 5 is a cross-sectional view of a band of the stent of Figure 1 having drug coatings thereon in accordance with a third exemplary embodiment of the present invention.

For example, intraocular lenses, placed to restore vision after cataract surgery is often compromised by the formation of a secondary cataract. The latter is often a result of cellular overgrowth on the lens surface and can be potentially minimized by combining a drug or drugs with the device. Other medical devices which often fail due to tissue in-growth or accumulation of proteinaceous material in, on and around the device, such as shunts for hydrocephalus, dialysis grafts, colostomy bag attachment devices, ear drainage tubes, leads for pace makers and implantable defibrillators can also benefit from the device-drug combination approach. Devices which serve to improve the structure and function of tissue or organ may also show benefits when combined with the appropriate agent or agents. For example, improved osteointegration of orthopedic devices to enhance stabilization of the implanted device could potentially be achieved by combining it with agents such as bone-morphogenic protein. Similarly other surgical devices, sutures, staples, vertebral disks, bone pins, suture anchors, hemostatic barriers, clamps, screws, plates, clips, vascular implants, tissue adhesives and sealants, tissue scaffolds, various types of dressings, bone substitutes, intraluminal devices, and vascular supports could also provide enhanced patient benefit using this drug-device combination approach. Essentially, any type of medical device may be coated in some fashion with a drug or drug combination which enhances treatment over use of the singular use of the device or pharmaceutical agent.

As stated previously, the implantation of a coronary stent in conjunction with balloon angioplasty is highly effective in treating acute vessel closure and may reduce the risk of restenosis. Intravascular ultrasound studies (Mintz et al., 1996) suggest that coronary stenting effectively prevents vessel constriction and that most of the late luminal loss after stent implantation is due to plaque growth, probably related to neointimal hyperplasia. The late luminal loss after coronary stenting is almost two times higher than that observed after conventional balloon angioplasty. Thus, inasmuch as stents prevent at least a portion of the restenosis process, a combination of drugs, agents or compounds which prevents smooth muscle cell proliferation, reduces

A stent is commonly used as a tubular structure left inside the lumen of a duct to relieve an obstruction. Commonly, stents are inserted into the lumen in a non-expanded form and are then expanded autonomously, or with the aid of a second device *in situ*. A typical method of expansion occurs through the use of a catheter-mounted angioplasty balloon which is inflated within the stenosed vessel or body passageway in order to shear and disrupt the obstructions associated with the wall components of the vessel and to obtain an enlarged lumen.

Figure 1 illustrates an exemplary stent 100 which may be utilized in accordance with an exemplary embodiment of the present invention. The expandable cylindrical stent 100 comprises a fenestrated structure for placement in a blood vessel, duct or lumen to hold the vessel, duct or lumen open, more particularly for protecting a segment of artery from restenosis after angioplasty. The stent 100 may be expanded circumferentially and maintained in an expanded configuration, that is circumferentially or radially rigid. The stent 100 is axially flexible and when flexed at a band, the stent 100 avoids any externally-protruding component parts.

The stent 100 generally comprises first and second ends with an intermediate section therebetween. The stent 100 has a longitudinal axis and comprises a plurality of longitudinally disposed bands 102, wherein each band 102 defines a generally continuous wave along a line segment parallel to the longitudinal axis. A plurality of circumferentially arranged links 104 maintain the bands 102 in a substantially tubular structure. Essentially, each longitudinally disposed band 102 is connected at a plurality of periodic locations, by a short circumferentially arranged link 104 to an adjacent band 102. The wave associated with each of the bands 102 has approximately the same fundamental spatial frequency in the intermediate section, and the bands 102 are so disposed that the wave associated with them are generally aligned so as to be generally in phase with one another. As illustrated in the figure,

drug/drug combination dosage at the desired location and in the desired amount.

In an alternate exemplary embodiment, the entire inner and outer surface of the stent 100 may be coated with drug/drug combinations in therapeutic dosage amounts. A detailed description of a drug for treating restenosis, as well as exemplary coating techniques, is described below. It is, however, important to note that the coating techniques may vary depending on the drug/drug combinations. Also, the coating techniques may vary depending on the material comprising the stent or other intraluminal medical device.

Rapamycin is a macroyclic triene antibiotic produced by streptomyces hygroscopicus as disclosed in U.S. Patent No. 3,929,992. It has been found that rapamycin among other things inhibits the proliferation of vascular smooth muscle cells *in vivo*. Accordingly, rapamycin may be utilized in treating intimal smooth muscle cell hyperplasia, restenosis, and vascular occlusion in a mammal, particularly following either biologically or mechanically mediated vascular injury, or under conditions that would predispose a mammal to suffering such a vascular injury. Rapamycin functions to inhibit smooth muscle cell proliferation and does not interfere with the re-endothelialization of the vessel walls.

Rapamycin reduces vascular hyperplasia by antagonizing smooth muscle proliferation in response to mitogenic signals that are released during an angioplasty induced injury. Inhibition of growth factor and cytokine mediated smooth muscle proliferation at the late GI phase of the cell cycle is believed to be the dominant mechanism of action of rapamycin. However, rapamycin is also known to prevent T-cell proliferation and differentiation when administered systemically. This is the basis for its immunosuppresive activity and its ability to prevent graft rejection.

polymeric matrix is in the range from about 1 micron to about 20 microns or greater.

The ethylene-co-vinylacetate, polybutylmethacrylate and rapamycin solution may be incorporated into or onto the stent in a number of ways. For example, the solution may be sprayed onto the stent or the stent may be dipped into the solution. Other methods include spin coating and RF- plasma polymerization. In one exemplary embodiment, the solution is sprayed onto the stent and then allowed to dry. In another exemplary embodiment, the solution may be electrically charged to one polarity and the stent electrically changed to the opposite polarity. In this manner, the solution and stent will be attracted to one another. In using this type of spraying process, waste may be reduced and more precise control over the thickness of the coat may be achieved.

Since rapamycin acts by entering the surrounding tissue, it s preferably only affixed to the surface of the stent making contact with one tissue. Typically, only the outer surface of the stent makes contact with the tissue. Accordingly, in a preferred embodiment, only the outer surface of the stent is coated with rapamycin.

The circulatory system, under normal conditions, has to be self-sealing, otherwise continued blood loss from an injury would be life threatening. Typically, all but the most catastrophic bleeding is rapidly stopped though a process known as hemostasis. Hemostasis occurs through a progression of steps. At high rates of flow, hemostasis is a combination of events involving platelet aggregation and fibrin formation. Platelet aggregation leads to a reduction in the blood flow due to the formation of a cellular plug while a cascade of biochemical steps leads to the formation of a fibrin clot.

Fibrin clots, as stated above, form in response to injury. There are certain circumstances where blood clotting or clotting in a specific area may pose a health risk. For example, during percutaneous transluminal coronary

heparin is then immobilized to this final layer and stabilized with sodium cyanoborohydride. This process is set forth in U.S. Patent Nos. 4,613,665; 4,810,784 to Larm and 5,049,403 to Larm et al.

Unlike rapamycin, heparin acts on circulating proteins in the blood and heparin need only make contact with blood to be effective. Accordingly, if used in conjunction with a medical device, such as a stent, it would preferably be only on the side that comes into contact with the blood. For example, if heparin were to be administered via a stent, it would only have to be on the inner surface of the stent to be effective.

In an exemplary embodiment of the invention, a stent may be utilized in combination with rapamycin and heparin to treat vascular disease. In this exemplary embodiment, the heparin is immobilized to the inner surface of the stent so that it is in contact with the blood and the rapamycin is immobilized to the outer surface of the stent so that it is in contact with the surrounding tissue. Figure 3 illustrates a cross-section of a band 102 of the stent 100 illustrated in Figure 1. As illustrated, the band 102 is coated with heparin 108 on its inner surface 110 and with rapamycin 112 on its outer surface 114.

In an alternate exemplary embodiment, the stent may comprise a heparin layer immobilized on its inner surface, and rapamycin and heparin on its outer surface. Utilizing current coating techniques, heparin tends to form a stronger bond with the surface it is immobilized to then does rapamycin. Accordingly, it may be possible to first immobilize the rapamycin to the outer surface of the stent and then immobilize a layer of heparin to the rapamycin layer. In this embodiment, the rapamycin may be more securely affixed to the stent while still effectively eluting from its polymeric matrix, through the heparin and into the surrounding tissue. Figure 4 illustrates a cross-section of a band 102 of the stent 100 illustrated in Figure 1. As illustrated, the band 102 is coated with heparin 108 on its inner surface 110 and with rapamycin 112 and heparin 108 on its outer surface 114.

coupling). In another exemplary embodiment, heparin may be photolinked on the surface, if it is appropriately grafted with photo initiator moieties. Upon application of this modified heparin formulation on the covalent stent surface, light exposure causes cross-linking and immobilization of the heparin on the coating surface. In yet another exemplary embodiment, heparin may be complexed with hydrophobic quaternary ammonium salts, rendering the molecule soluble in organic solvents (e.g. benzalkonium heparinate, troidodecylmethylammonium heparinate). Such a formulation of heparin may be compatible with the hydrophobic rapamycin coating, and may be applied directly on the coating surface, or in the rapamycin/hydrophobic polymer formulation.

It is important to note that the stent may be formed from any number of materials, including various metals, polymeric materials and ceramic materials. Accordingly, various technologies may be utilized to immobilize the various drugs, agent, compound combinations thereon. In addition, the drugs, agents or compounds may be utilized in conjunction with other percutaneously delivered medical devices such as grafts and profusion balloons.

In addition to utilizing an anti-proliferative and anti-coagulant, anti-inflammatories may also be utilized in combination therewith. One example of such a combination would be the addition of an anti-inflammatory corticosteroid such as dexamethasone with an anti-proliferative, such as rapamycin, cladribine, vincristine, taxol, or a nitric oxide donor and an anti-coagulant, such as heparin. Such combination therapies might result in a better therapeutic effect, i.e., less proliferation as well as less inflammation, a stimulus for proliferation, than would occur with either agent alone. The delivery of a stent comprising an anti-proliferative, anti-coagulant, and an anti-inflammatory to an injured vessel would provide the added therapeutic benefit of limiting the degree of local smooth muscle cell proliferation, reducing a stimulus for proliferation, i.e., inflammation and reducing the effects of coagulation thus enhancing the restenosis-limiting action of the stent.

the drugs, agents or compounds to simply delaminate from the stent through contact with the balloon or via expansion. Therefore, prevention of this potential problem is important to have a successful therapeutic medical device, such as a stent.

There are a number of approaches that may be utilized to substantially reduce the above-described problem. In one exemplary embodiment, a lubricant or mold release agent may be utilized. The lubricant or mold release agent may comprise any suitable biocompatible lubricious coating. An exemplary lubricious coating may comprise silicone. In this exemplary embodiment, a solution of the silicone base coating may be introduced onto the balloon surface, onto the polymeric matrix, and/or onto the inner surface of the sheath of a self-expanding stent delivery apparatus and allowed to air cure. Alternately, the silicone based coating may be incorporated into the polymeric matrix. It is important to note, however, that any number of lubricious materials may be utilized, with the basic requirements being that the material be biocompatible, that the material not interfere with the actions/effectiveness of the drugs, agents or compounds and that the material not interfere with the materials utilized to immobilize the drugs, agents or compounds on the medical device. It is also important to note that one or more, or all of the above-described approaches may be utilized in combination.

Referring now to Figure 6, there is illustrated a balloon 200 of a balloon catheter that may be utilized to expand a stent *in situ*. As illustrated, the balloon 200 comprises a lubricious coating 202. The lubricious coating 202 functions to minimize or substantially eliminate the adhesion between the balloon 200 and the coating on the medical device. In the exemplary embodiment described above, the lubricious coating 202 would minimize or substantially eliminate the adhesion between the balloon 200 and the heparin or rapamycin coating. The lubricious coating 202 may be attached to and maintained on the balloon 200 in any number of ways including but not limited to dipping, spraying, brushing or spin coating of the coating material from a solution or suspension followed by curing or solvent removal step as needed.

402. Accordingly, upon deployment of the stent 400, the lubricious coating 404 preferably minimizes or substantially eliminates the adhesion between the sheath 402 and the drug, agent or compound coated stent 400.

In an alternate approach, physical and/or chemical cross-linking methods may be applied to improve the bond strength between the polymeric coating containing the drugs, agents or compounds and the surface of the medical device or between the polymeric coating containing the drugs, agents or compounds and a primer. Alternately, other primers applied by either traditional coating methods such as dip, spray or spin coating, or by RF-plasma polymerization may also be used to improve bond strength. For example, as shown in Figure 9, the bond strength can be improved by first depositing a primer layer 500 such as vapor polymerized parylene-C on the device surface, and then placing a second layer 502 which comprises a polymer that is similar in chemical composition to the one or more of the polymers that make up the drug-containing matrix 504, e.g., polyethylene-co-vinyl acetate or polybutyl methacrylate but has been modified to contain cross-linking moieties. This secondary layer 502 is then cross-linked to the primer after exposure to ultra-violet light. It should be noted that anyone familiar with the art would recognize that a similar outcome could be achieved using cross-linking agents that are activated by heat with or without the presence of an activating agent. The drug-containing matrix 504 is then layered onto the secondary layer 502 using a solvent that swells, in part or wholly, the secondary layer 502. This promotes the entrainment of polymer chains from the matrix into the secondary layer 502 and conversely from the secondary layer 502 into the drug-containing matrix 504. Upon removal of the solvent from the coated layers, an interpenetrating or interlocking network of the polymer chains is formed between the layers thereby increasing the adhesion strength between them. A top coat 506 is used as described above.

A related problem occurs in medical devices such as stents. In the drug-coated stents crimped state, some struts come into contact with each other and when the stent is expanded, the motion causes the polymeric

WHAT IS CLAIMED IS:

1. A local drug delivery apparatus comprising:

a medical device for implantation into a treatment site of a living organism;

at least one agent in therapeutic dosages releasably affixed to the medical device for the treatment of reactions by the living organism caused by the medical device or the implantation thereof; and

a material for preventing the at least one agent from separating from the medical device prior to implantation of the medical device at the treatment site, the material being affixed to at least one of the medical device or a delivery system for the medical device.

2. The local drug delivery apparatus according to Claim 1, wherein the medical device comprises an intraluminal medical device.

3. The local drug delivery apparatus according to Claim 2, wherein the intraluminal medical device comprises a stent.

4. The local drug delivery apparatus according to Claim 1, wherein the at least one agent comprises an anti-proliferative.

5. The local drug delivery apparatus according to Claim 1, wherein the at least one agent comprises an anti-inflammatory.

6. The local drug delivery apparatus according to Claim 1, wherein the at least one agent comprises an anti-coagulant.

7. The local drug delivery apparatus according to Claim 1, wherein the at least one agent comprises an immunosuppressant.

18. A local drug delivery apparatus comprising:

a medical device for implantation into a treatment site of a living organism;

at least one agent in therapeutic dosages releasably affixed to the medical device for the treatment of reactions by the living organism caused by the medical device or the implantation thereof, the at least one agent being incorporated into a polymeric matrix; and

a material for preventing the at least one agent from separating from the medical device prior to implantation of the medical device at the treatment site, the material being affixed to at least one of the medical device or a delivery system for the medical device.

19. The local drug delivery apparatus according to Claim 18, wherein the medical device comprises an intraluminal medical device.

20. The local drug delivery apparatus according to Claim 19, wherein the intraluminal medical device comprises a stent.

21. The local drug delivery apparatus according to Claim 20, wherein the polymeric matrix comprises ethylene-co-vinylacetate and polybutylmethacrylate.

22. The local drug delivery apparatus according to Claim 20, wherein the polymeric matrix comprises ethylene-co-vinylacetate and polybutylmethacrylate.

23. The local drug delivery apparatus according to Claim 20, wherein the material for preventing the at least one agent from separating from the medical device comprises a lubricious coating.

31. The local drug delivery apparatus according to Claim 30 wherein the material for preventing the polymeric matrix from adhering to itself comprises a water soluble powder.

32. The local drug delivery apparatus according to Claim 31 wherein the water soluble powder is affixed to the surface of the polymeric matrix.

33. The local drug delivery apparatus according to Claim 32 wherein the water soluble powder comprises an anti-oxidant.

34. The local drug delivery apparatus according to Claim 32 wherein the water soluble powder comprises anti-coagulant.

35. A drug delivery device comprising:

a medical device for implantation into a treatment site of a living organism; and

therapeutic dosages of one or more anti-proliferatives, one or more anti-inflammatories, one or more anti-coagulants, and one or more immunosuppressants releasably affixed to the medical device for the treatment of reactions by the living organism caused by the medical device or the implantation of the medical device at the treatment site.

36. The drug delivery device according to Claim 35, further comprising therapeutic dosages of modified genes via one or more non-viral gene introducers releasably affixed to the medical device.

37. The drug delivery device according to Claim 36, further comprising a material for preventing the therapeutic dosages releasably affixed to the medical device from separating from the medical device during delivery and implantation of the medical device at the treatment

affixing one or more agents comprises incorporating the agents in at least one polymer and coating the medical device with the at least one polymer.

44. The method for maintaining agents on a medical device during implantation according to Claim 43, wherein the step of treating one of the medical device or the delivery device comprises coating the at least one polymer with a lubricious material.

45. The method for maintaining agents on a medical device during implantation according to Claim 43, wherein the step of treating one of the medical device or the delivery device comprises coating the delivery device with a lubricious material.

46. The method for maintaining agents on a medical device during implantation according to Claim 43, wherein the step of treating one of the medical device or the delivery device comprises incorporating a lubricious material into the polymer.

47. The method for maintaining agents on a medical device during implantation according to Claim 43, wherein the step of treating one of the medical device or the delivery device comprises coating the at least one polymer with a water soluble powder.

48. A method for maintaining agents on a medical device during implantation into a treatment site of a living organism comprising:

releasably affixing one or more agents in therapeutic dosages to the medical device by incorporating the one or more agents in at least one polymer;

treating the medical device with a material for preventing the polymer from adhering to itself when parts of the medical device make contact; and

loading the medical device into a delivery device.

FIG. 1

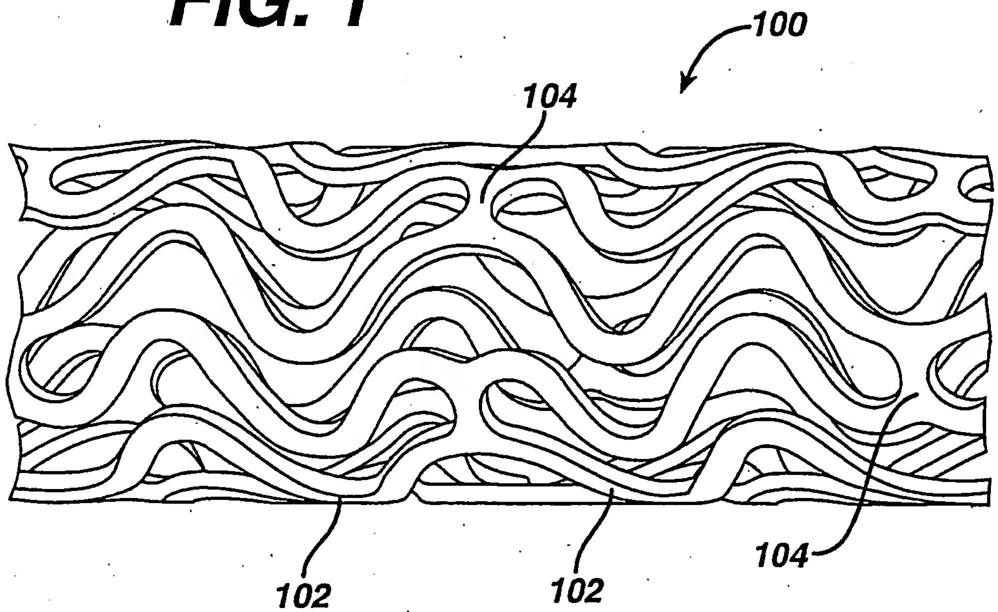


FIG. 2

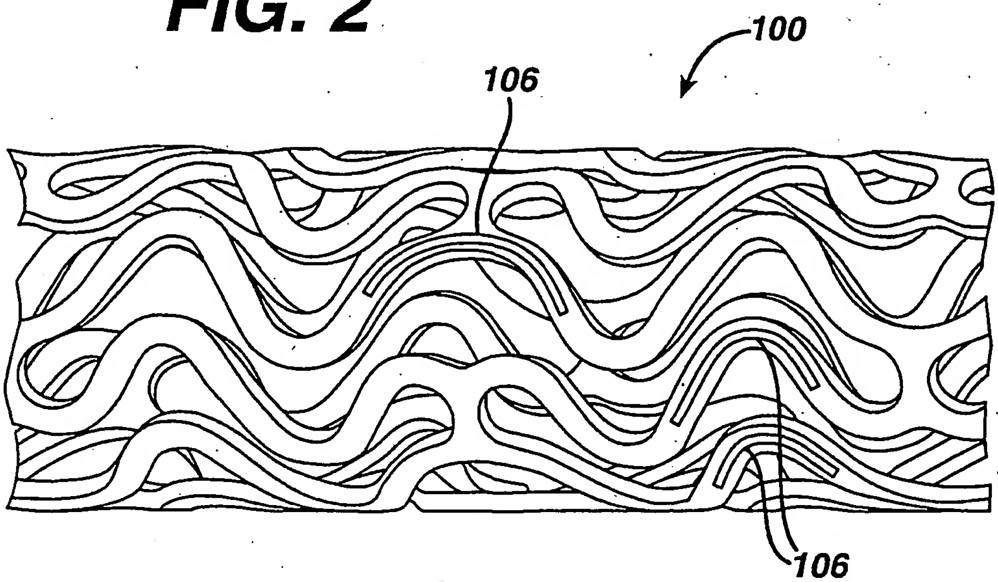


FIG. 6

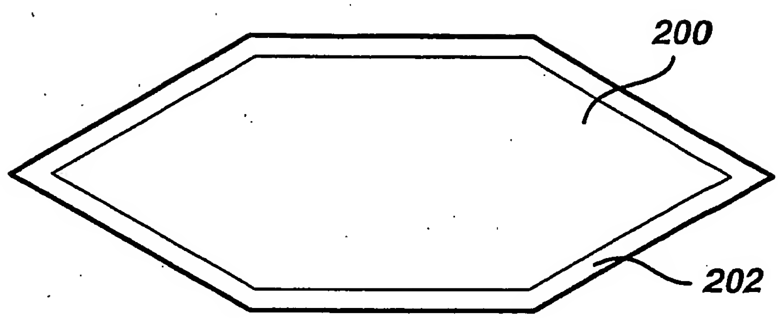


FIG. 7

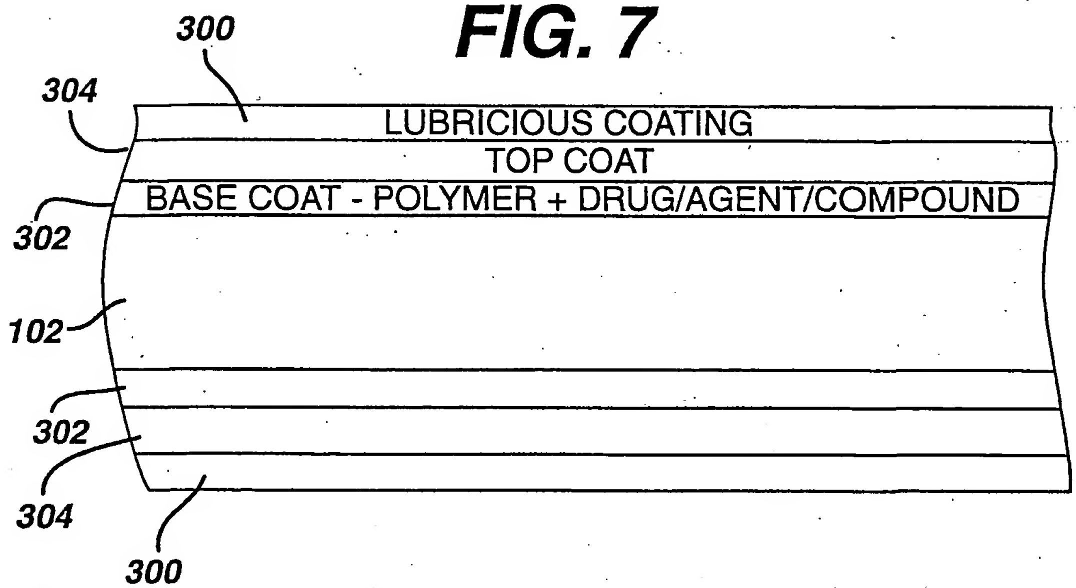
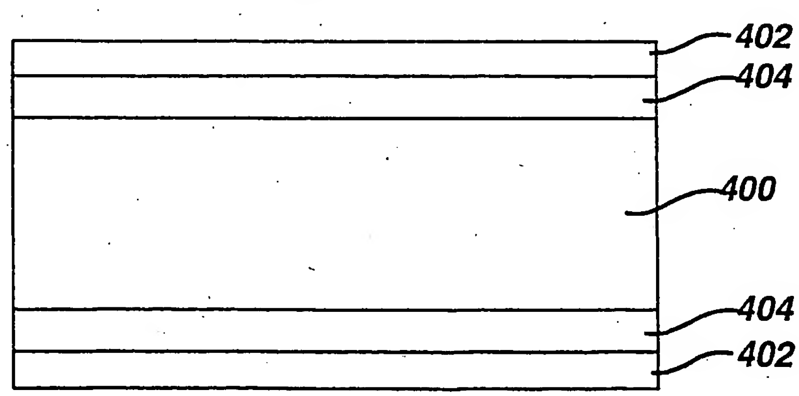


FIG. 8



INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 02/19889

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61L31/16 A61F2/06

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61F A61L A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, PAJ, WPI Data, COMPENDEX, INSPEC

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 98 36784 A (COOK INC) 27 August 1998 (1998-08-27) page 5, line 26 -page 7, line 14 page 12, line 14 -page 13, line 27 claims ———	1-51
X	WO 00 32255 A (SCIMED LIFE SYSTEMS INC) 8 June 2000 (2000-06-08) page 13, line 13 -page 14, line 12 claims ———	1-51
A	WO 00 27445 A (SCIMED LIFE SYSTEMS INC) 18 May 2000 (2000-05-18) page 12, line 1 -page 13, line 2 claims ———	1-51
	-/--	

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
15 October 2002	22/10/2002

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Thornton, S

Form PCT/ISA/210 (second sheet) (July 1992)

International application No.
PCT/US 02/19889

INTERNATIONAL SEARCH REPORT

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: –
because they relate to subject matter not required to be searched by this Authority, namely:
see FURTHER INFORMATION sheet PCT/ISA/210

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

Patent document cited in search report		Publication date	Patent family member(s)			Publication date
WO 9836784	A	27-08-1998	AU	737252	B2	16-08-2001
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